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(71) Applicant *(for all designated States except US)*: AKTIEBOLAGET ASTRA [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)* : JONDAL, Mikael [SE/SE]; Strandvägen 53, S-115 23 Stockholm (SE). ROSÉN, Anders [SE/SE]; Gustafsvägen 17, S-171 49 Solna (SE).

(74) Agents: MIKSCHE, Gerhard et al.; AB Astra, Patent and Trademark Department, S-151 85 Södertälje (SE).

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(54) Title: METHOD FOR THERAPY OF LEUKEMIAS AND CERTAIN OTHER MALIGNANCIES

(57) Abstract

A method for the treatment of malignantly transformed cells in animals and man, which comprises the administration of a therapeutically adequate amount of specified B-cell growth and differentiation factors.

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Method for therapy of leukemias and certain other malignancies

Field of the invention

The present invention relates to a novel strategy for the treatment of B lymphocyte leukemia and certain other malignant diseases.

The use of B-cell growth factors, and antibodies that mimic these, can be used for the induction of differentiation in certain malignant disorders. We describe here the use of these factors, and antibodies. Firstly their definition and secondly the strategy of use, either alone or in combination with co-factors, so-called competence inducing agents.

General outline of the invention and introduction

Cancer cells are characterized by uncontrolled growth. For some time there has been a concept that growth can be suppressed by inducing these cells to differentiate into a non-proliferative state. Clinical trials have also been done in different leukemias with differentiation-inducing agents such as vitamins and interferons. However, no such trials have been done with more specific growth and differentiation factors, or antibodies, which only react with defined receptor structures. The present invention proposes to use such specific factors for cancer treatment, either alone or in combination with supporting, non-specific agents.

The development of normal cells into cancer cells is a multi-step process. During malignant transformation some cell types, for example some B lymphocytes (reference 1), acquire the ability to express receptors for defined growth factors and respond to these by proliferation or maturation. Receptor expression is one important step in the progression towards a fully malignant phenotype. The tumor cells are thus "frozen" at a specific differentiation stage. This block is, however, not irreversible. We here present method for the use of specified B-cell growth factors, and monoclonal antibodies binding to

corresponding receptor structures, to be used alone or in common with co-factors, for the induction of terminally differentiated cells (end cells) which do not further divide. The growth factors and co-factors are described. The strategy of clinical treatment is exemplified with B-cell chronic lymphocytic leukemias (B-CLL), which were induced to further differentiation (to a more mature stage) signified by impaired capacity to proliferate and the expression ofa plasmacytoid morphology, as judged by surface markers, cytoplasmic immunoglobulin, and endoplasmatic reticulum.

To grasp the concept of differentiation therapy it is important to understand how normal cells develop. In the bone marrow, different functionally specialized cell types develop as a result of differentiation (committment) of the multipotent stem cells. This differentiation gives rise to precursors of various cell linages (B-cell linage, T-cell linage, myeloid linage). Subsequent phenotypic changes of such unipotent cells into end cells is called maturation or terminal differentiation. The activation of human B-cells from a resting stage, leading into further differentiation and maturation and the terminal stage proceeds through at least two steps.

1) The triggering step, where the cells are exposed to activating factors, so-called competence inducing agents. For the B-cell series these are: Antigens; anti-immunoglobulins (anti-idiotypes); interleukin 1, 2 and 3 and sub-components thereof, interleukin 4 (IL4) and antibodies to the IL4-receptor; reagents acting on the C3d-receptor (CD11c), such as polymerized complement 3d or antibodies to the C3d receptor (anti-gp140); anti-gp35 (CD20). Phorbol esters, such as TPA or PMA are used experimentally in vitro as potent competence-inducing agents, but these can however only serve as models since they are toxic and incompatible with clinical use. The phorbol esters act on protein kinase C (PKC) and in their function mimic biologically active agents. Other experimental competence-inducing agents of importance are: solid phase protein-A; inactivated Staphylococcus Aureus Cowan I (SAC); Poke weed Mitogen (PWM); non-transforming or inactivated Epstein-Barr Virus (EBV) (from the non-transforming strain P3HR1 or UV-inactivated virus) lipopolysaccharides (LPS).

2) The progression step. The triggering step induces receptors for various progression signals such as : IL-2; B-cell growth factor II or TRF, now called IL5; low molecular weight BCGF (12K BCGF); Namalwa-derived 60K BCGF; antibodies to CD23 (a p45 protein expressed on the B-cell surface of IgM+, IgD+ cells, and a potential receptor for 12K BCGF); antibodies to CDw40, a p50 antigen present on B-cells and on urinary bladder carcinoma cells, but also on cervical and lung carcinoma cells (reference 2), furthermore BSF2 (previously called B-cell differentiation factor (BCDF).

The following list is a brief explanation of abbreviations used in the present specification.

BCDF: B-cell differentiation factor
BCGF: B-cell growth factor
B-CLL: B-cell chronic lymphocytic leukemia
BSF: B-cell stimulating factor
C3d: Sub-component of complement factor C3
CD23: A p45 protein expressed on cells of the B-lymphocyte linage, particularly IgM and IgD positive cells
CDw40: A p50 protein expressed on B-cells and on bladder carcinoma cells
EBV: Epstein-Barr virus
gp35: Glycoprotein 35K molecular weight, belonging to the CD20 group (cluster of differentiation group)
gp140: Glycoprotein 140K molecular weight, with C3d-receptor function
IgD: Immunoglobulin class D
IgM: Immunoglobulin class M
IL-1, IL-2, IL-3, IL-4, IL-5: Interleukin 1, 2, 3, 4, 5
LPS: Lipopolysaccharides
Molt4: A T-lymphoma derived cell line
p45: A 45K molecular weight membrane protein
PMA: 4-phorbol 12-myristate 13-acetate
PWM: Poke weed mitogen
SAC: Staphylococcus aureus Cowan I
Solid phase protein-A: Matrix (Sepharose for example) -bound protein-A
TPA: Tumor promoting agent
TRF: T-cell replacing factor

T-T hybridoma: A somatic cell hybrid between two different T-cells

Detailed description of the invention

The present invention relates to a novel method for the treatment of such malignantly transformed cells in mammals and in man, which express receptors for growth factors and differentiation factors as listed in Table 2 below. The method is characterized by the administration of therapeutically adequate amounts of one or several growth and differentiation factors selected from those listed in Table 2. If necessary, said factor is administered following a period of pre-treatment with a co-factor capable of inducing the malignantly transformed cells to express receptors for the factors described in Table 2. Example of such co-factors, which are called competence inducing agents, are given in Table 1 below. It is foreseen that the administration of a factor as described in Table 2 can be made simultaneously with the co-factor.

More precisely, the novel method of treatment by the present invention can be applied to stem-cell disorders, hematopoetic malignancies, for example leukemias, B-cell leukemias and B-cell chronic lymphocytic leukemias, and other tumors which express receptors and respond to the described growth factors. For example, bladder carcinomas expressing the CDw40 antigen can potentially be treated in the described fashion. All the factors and co-factors listed in Table 2 and Table 1 are substances which are known as such. They are, however, not in every instance known to have therapeutic utility.

The choice of a suitable co-factor is no critical parameter of the invention. There are experimental methods available which will enable the skilled worker to establish whether a specific co-factor has the capacity to induce receptors, as those described above and in Table 2, in malignantly transformed cells.

The invention in another aspect relates to a growth and stimulating factor according to Table 2 for use in the treatment of malignantly

transformed cells in animals and in man, in particular for use in such malignantly transformed cells which express receptors for growth and differentiation factors according to Table 2. Also in this aspect, if necessary, the factor according to Table 2 is administered following a period of pre-treatment with a co-factor as described, which is capable of inducing the malignantly transformed cells to express receptors for the factors described in Table 2. Another aspect of the invention relates to the use of growth and differentiation factors as described in Table 2 in the preparation of a medicament for treatment of malignancies. Such a medicament may comprise a co-factor as described above. Even though the individual factors according to Table 2 as well as co-factors as exemplified in Table 1 are known in the art, pharmaceutical preparations containing a factor according to Table 2 or of a combination of a factor according to Table 2 and a co-factor according to Table 1, are novel and represent as such an additional aspect of the present invention.

In clinical practice, the factors, co-factors or combinations thereof are administered in a manner which is analogous with known ways of administering medicaments for the treatment of cancer. Thus, administration will preferably be made by infusion or by intramuscular deposition.

The amount in which the factor and/or co-factors is administered will vary within a wide range and will depend on various circumstances such as the severity of the disease and the age and the state of the patient. As an example of a suitable dosage interval can be mentioned from 10 000 to 300 000 Units (U) of growth and differentiation factor per kg bodyweight per 24 hours. An amount of 200 000 U per kg bodyweight and per 24 hours will sometimes be adequate.

The following Table 1 gives a list which exemplifies co-factors which may be used. The designation E indicates that the co-factor mainly is experimental and has possible use for diagnostic purposes. The designation C indicates that the co-factor has clinical use.

Table 1. Co-factors (Competence inducing agents)

E Phorbol esters such as TPA
E Antigens
C Anti-Immunoglobulins (anti-idiotypes)
C Interleukin 1 and sub-components thereof
C Interleukin 2 and sub-components thereof
C Interleukin 3 and sub-components thereof
C Interleukin 4 (BSF1)
C Anti-IL4-receptor antibodies
E Poke weed mitogen
E Lipopolysaccharides
E Epstein Barr virus, non-transforming or inactivated
C C3d receptor (CD11c) reactive agents C' and anti-receptor (gp 140) antibodies
C Anti-gp35 (CD20)
E SAC, Inactivated Staphylococcus aureus Cowan I
E Solid-phase protein A
C Interferons (alfa, beta and gamma)
C Vitamins (in particular vitamin A, D, and biologically active derivatives

The following Table 2 lists the growth and differentiation factors which are used according to the invention. All listed factors have clinical use.

Table 2. B-cell Growth and Differentiation Factors (progression signals)

BCGF 12K and high molecular weight BCGF derived from T-helper cells and T-T hybridomas
BCGF 30K (clevage product of the CD23) derived from B-cell lines
BCGF 60K derived from the Namalwa cell line
BSF2 also called BCDF
Interleukin 5, previously called BCGF II or TRF
Anti-CD23 antibodies

Anti-CDw40 (p50) antibodies, present on B-cells and bladder carcinoma cells
Anti-BCGF receptor antibodies
Gamma-interferon
Interleukin 2 and sub-components thereof

Definition of the B-cell growth factors

The producer cells of the BCGF's can be T-helper cells immortalized by somatic cell hybridization with a T-lymphoma called Molt4. One of these BCGF-producer cell lines (T-T-hybridoma MP6) are described in detail in reference 3.

The biochemical properties of this BCGF are:

1) Ammonium sulphate precipitable at 80-90% saturation, 0°C
2) Heat labile at 56°C, 30 min.
3) Protease sensitive
4) Glycoprotein nature, with binding capacity to mannose-specific lectins
5) HPLC-gelfiltration analysis gives an apparent molecular weight of 12-14K, as well as high molecular weight component

Biological properties

The growth and differentiation factors according to Table 2 stimulate the proliferation and differentiation of normal and B-CLL lymphocytes pretreated or co-treated with co-factors as shown in Table 1 (anti-IgM, SAC, TPA).

Target cells in clinical situations:

Target cells in clinical situations are all such malignantly transformed cells that express receptors for factors according to Table 2 and respond to these factors by differentiation, including all those malignant cells that can be induced to express receptors for the factors described in Table 2 and respond to these. Such induction can be exerted by the co-factors described in Table 1 or by other means.

Experimental evidence

Several B chronic lymphocytic leukemias were investigated for their capacity to respond to BCGF by the method described in reference 3. As model agents we used TPA, SAC and anti-IGM as co-factors and as growth factors a T-T hybridoma produced BCGF.

Figure 1 shows one representative stimulation experiment leading to induced differentiation as well as to a transient peak of proliferation. In this particular experiment the co-factor was TPA and the growth factor T-T hybridoma derived BCGF. TPA alone does not give the wanted effect.

Figure 2 details the differentiation induction and proliferation using SAC as co-factor and BCGF as growth factor.

The vertical axis (Transformation index) designates the quotient between test and control cpm of incorporated ^{3}H-thymidine. Each cell population was analyzed at the indicated time points for plasmacytoid properties and at the end of the experiment the vast majority of the cells expressed plasmacytoid properties according to the method described in reference 4. This clearly shows that the induction of terminal differentiation (maturation) was taking place as a result of activation (a short transient peak of proliferation) exerted by co-factors and factors described in Tables 1 and 2. Accordingly, the cells have lost their growth potential and consequently their malignant characteristics.

The response of B-CLL leukemic cells to a B-cell growth factor derived from T-T hybridoma MP6 in combination with co-factors IL-1 and IL-2 is described in the following Table 3. B-CLL cells do not respond to B-cell growth factor, IL-2 or IL-1 alone but gives an optimal response when these three factors are combined (stimulation index 55.5).

Table 3. Response of B-CLL leukemic cells to a B-cell growth factor, derived from T-T hybridoma MP6, in combination with co-factors IL1 and IL2

B-cell growth factor	Co-factor	Response of B-CLL leukemic cells cpm[§]	SI[£]
MP6	-	241	below 1
-	IL-1	161	below 1
-	IL-2	256	below 1
-	IL-1 and IL-2	373	below 1
MP6	IL-1	456	below 1
MP6	IL-2	5 988	11.6
MP6	IL-1 and IL-2	28 550	55.5
Medium control	-	514	-

Legend: [§] Isolated B-CLL leukemic cells were stimulated as described in reference 3. The response was measured in incorporation of ^{3}H-thymidine at 72 h.

[£] SI = stimulation index, experimental value divided by back-ground control.

Strategy of therapy

1) Compounds in Table 2 by themselves should be administered when malignant cells already express any of the receptors for the factors shown in Table 2

2) Compounds in Table 1 plus compounds in Table 2 should be administered in combination when the malignant cells do not express any of the receptors for the factors according to Table 2. This includes any of the specific compounds listed.

References

1) Gordon J, Aman P, Rosén A, et al. Int. J. Cancer 1984, 35, 251.
2) Paulie S, et al. Cancer Immunol Immunotherapy 1985, 20, 23.
3) Rosén et al. Lymphokine Research 1986, 5, 185.
4) Anismova E, Saemundsen A, Roubal J, Vonka V, and Klein G.J. Gen Virol 1982, 58, 63.

What we claim is:

1. A method for the treatment of malignantly transformed cells in animals and man, which comprises the administration of a therapeutically adequate amount of a B-cell growth and differentiation factor selected from

(a) BCGF 12K and high molecular weight BCGF derived from T-helper cells and T-T-hybridomas

(b) BCGF 30K (cleavage product of the CD23) derived from B-cell lines

(c) BCGF 60K derived from the Namalwa cell line

(d) BSF2, also called BCDF

(e) Interleukin 5, previously called BCGF II or TRF

(f) Anti-CD23 antibodies

(g) Anti-CDw40 (p50) antibodies present on B-cells and bladder carcinoma cells, and

(h) Anti-BCGF receptor antibodies.

(i) Gamma-interferon

(j) Interleukin 2 and sub-components thereof

2. A method according to claim 1, characterized in that the malignantly transformed cells are pre-treated with a co-factor capable of inducing the said malignantly transformed cells to express receptors for the factors (a)-(j) in claim 1.

3. A method according to claim 2, characterized in that the said co-factor is selected from

(a) anti-immunoglobulins (anti-idiotypes)
(b) interleukin 1 and sub-components thereof
(c) interleukin 2 and sub-components thereof
(d) interleukin 3 and sub-components thereof
(e) interleukin 4 (BSF1)
(f) anti-IL4-receptor antibodies
(g) C3d receptor (CD11c) reactive C'agents and anti-receptor (gp 140) antibodies
(h) anti-gp35 (CD20)
(i) interferons (alfa, beta and gamma)
(j) vitamins

4. A method according to any of claims 1-3 for the treatment of stem cell disorders.

5. A method according to any of claims 1-3 for the treatment of hematopoetic malignancies.

6. A method according to any of claims 1-3 for the treatment of B-cell leukemias.

7. A method according to any of claims 1-3 for the treatment of B-cell chronic lymphocytic leukemia.

8. A method according to any of claims 1-3 for the treatment of other tumors which express receptors for, and respond to, factors as described in claim 1.

9. A B-cell growth and differentiating factor as listed under (a)-(j) in claim 1 for use in the treatment of malignantly transformed cells in animals and man.

10. A B-cell growth and differentiating factor as listed under (a)-(j) in claim 1 for use in the treatment of the disorders mentioned in claims 4, 5, 6, 7, and 8.

11. A B-cell growth and differentiating factor for use according to claims 9 and 10 in conjunction with a co-factor capable of inducing the malignantly transformed cells to express receptors for a growth and differentiation factor as listed under (a)-(j) in claim 1.

12. A B-cell growth and differentiating factor for use according to claim 12, in conjunction with a co-factor as listed under (a)-(j) in claim 3.

13. A B-cell growth and differentiating factor as listed under (a)-(j) in claim 1 for use in therapy, optionally in conjunction with a co-factor capable of inducing malignantly transformed cells to express receptors for the said factors (a)-(j).

14. A pharmaceutical composition, comprising as active ingredient a B-cell growth and differentiating factor as listed under (a)-(j) in claim 1.

15. A pharmaceutical composition according to claim 14, comprising also a co-factor capable of inducing malignantly transformed cells to express receptors for the said factors (a)-(j).

16. The use of a B-cell growth and differentiation factor as listed under (a)-(j) in claim 1 in the preparation of a medicament for the treatment of malignantly transformed cells in animals and man.

17. The use of a B-cell growth and differentiation factor as listed under (a)-(j) in claim 1 in the preparation of a medicament for the treatment of the disorders mentioned in claims 4, 5, 6, 7, and 8.

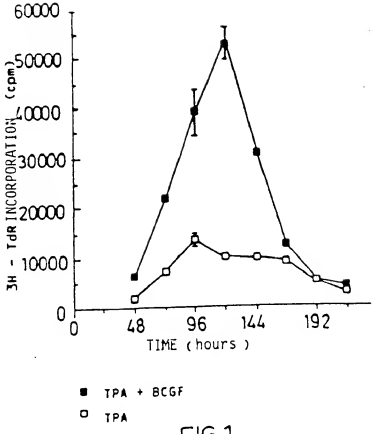
60000
50000
40000
30000
20000
10000
0
3H - TdR INCORPORATION (cpm)
0
48
96
144
192
TIME (hours)
TPA + BCGF
TPA

FIG. 1

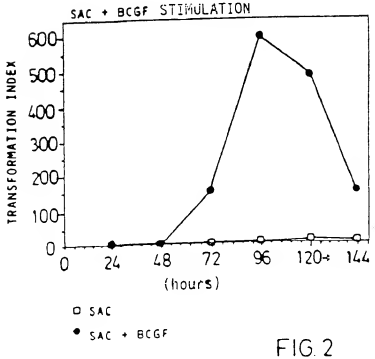
SAC + BCGF STIMULATION
600
500
400
300
200
100
0
TRANSFORMATION INDEX
0
24
48
72
96
120
144
(hours)
SAC
SAC + BCGF

FIG. 2

INTERNATIONAL SEARCH REPORT

International Application No PCT/SE88/00118

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [6]

According to International Patent Classification (IPC) or to both National Classification and IPC 4

A 61 K 39/00, 37/02, 35/12

II. FIELDS SEARCHED

Minimum Documentation Searched [7]	
Classification System	Classification Symbols
IPC	A 61 K 35/12,/14,/16,/26, 37/02,/04, 39/00,/395; C 12 N 5/00
US Cl	424:85, 88, 101; 514:2, 21, 885

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [8]

SE, NO, DK, FI classes as above

III. DOCUMENTS CONSIDERED TO BE RELEVANT [9]

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No. [13]
Y	EP, A1, 0 248 516 (CETUS CORPORATION) 9 December 1987 See in particular p. 1-5 and claims & JP, 62242629	1-17
Y	Immunological Reviews, No 99, p. 241-262 published 1987 (Lernhardt W et al) "Control of the Cell Cycle of Murine B Lymphocytes: The Nature of a- and Δ-B-Cell Growth Factors and of B-Cell Maturation Factors"	1-17
X,E	WO, A1, 87/02990 (SCHERING-BIOTECH CORPORATION) 21 May 1987 See in particular p 7, last 11 lines, p. 9 third paragraph, p. 44, second paragraph & EP, 0249613	1,9,10,13,14, 16,17
X,E	EP, A2, 220 045 (MITSUITOATSU CHEMICALS INCORPORATED) 29 April 1987 See claims 8 and 9 & JP, 62087090	1,9,10,13,14, 16,17

* Special categories of cited documents: [10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
1988-06-03	1988 -06- 0 6
International Searching Authority	**Signature of Authorized Officer [14]**
Swedish Patent Office	Carl Olof Gustafsson

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE *

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 1-8, because they relate to subject matter not required to be searched by this Authority, namely:

Methods for the treatment of the human or animal body by means of therapy, see Rule 39.1.

2. [ ] Claim numbers..... because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claim numbers....., because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. [X] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING *

This International Searching Authority found multiple inventions in this international application as follows:

A posteriori, the claims were found to consist of several inventions.

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

4. [X] As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	EP, A2, 077 571 (AJINOMOTO CO., INC) 27 April 1983 See p 3, line 13 - p 4, line 11 & JP, 58067193 JP, 58067187	1,9,10,13, 14,16,17
Y	EP, A2, 210 461 (AJINOMOTO CO, INC) 4 February 1987 See in particular col 1, line 5-9 & JP, 62240700 JP, 62234097	1-17
X,E	WO, A1, 87/04466 (AMERSHAM INTERNATIONAL PLC /GB/GB/) 30 July 1987 & EP, 0256042	1,9,10,13, 14,16,17
Y	Läkartidningen Vol. 82, p 2798-2800, publ 1985 (Ernström U) "Tillväxt och differentiering hos B-lymfocyter".	1-17
A	Nature Vol. 319, p 620, publ 20 February 1986, (Cambier J C) "Seeing the way to B-cell Growth"	1-17
Y	Chemical Abstracts Vol 106 (1987) abstract No 65853g, Jpn Kokai Tokkyo Koho JP 61, 243, 029, /86, 243, 029/	1-7
X	Patent Abstract of Japan, Vol 8, No 205 (C-243) abstract of JP 59-95220, published 1 June 1984	1-17